The Institute for Safe Medication Practices
A Nonprofit Organization Educating the Healthcare Community and Consumers About Safe Medication Practices

QuarterWatch: 2008 Quarter 2

January 15, 2009

Executive Summary

Reports of serious injury, disability, and death associated with drug therapy exceeded 20,000 cases for a second consecutive quarter in 2008. For the first half of 2008, the number of serious adverse drug events reported to the Food and Drug Administration was 40% higher than the average for the four quarters of 2007.

In the second quarter, two drugs contributed substantially to the increase for the first time. A massive recall of the heart drug digoxin—affecting 60% of the nation's supply—helped spur reports of at least 650 patient deaths--but a direct link to defective tablets was difficult to assess. In addition, reports of serious injuries for the asthma drug montelukast (Singulair) among children and adults grew seven-fold in the quarter following an FDA public notice that it was studying a possible link between the drug and aggressive and suicidal behavior.

The ISMP QuarterWatch pilot monitoring program evaluates computer excerpts of all serious, disabling and fatal adverse drug events reported to the FDA for patients in the United States. The U.S. system for postmarket safety surveillance relies on voluntary reports from consumers and health professionals, and the submission of such a report does not in itself prove that the suspect drug caused the event described. It is not known what percentage of all such events that occur are voluntarily reported, although available data show only a small fraction of patient injuries associated with drug therapy are ever reported.

The highlights of the second quarter of 2008 (April-June) are as follows:

Trends over Time

- In the second quarter of 2008, the FDA received 22,980 reports of serious injury associated with drug therapy, including 2968 deaths and 585 cases of disability or birth defect. The total also included 1397 cases attributed to medication error.
- The 2968 reported patient deaths in the second quarter declined from a record 4824 in the previous quarter, but remained substantially higher than in the previous year.
- Plotting time trends for serious injuries was complicated by a technical clarification by the FDA which permitted capturing 2109 additional serious injury cases that would not have been detected using previous QuarterWatch criteria. Without this technical change, serious injuries, disability and death combined were similar to the previous quarter—an increase of 126 cases.

Signals for Specific Drugs

Digoxin (DIGITEK brand)

The most striking signal seen was for the generic heart drug digoxin, which accounted for 1882 reports of serious injury, including 650 patient deaths—more cases than for any other prescription drug in the second quarter. Digoxin is used by more than one million patients with heart failure—a medical condition in which the declining output of the heart is causing serious medical problems.

We linked the majority of these reports—and others from earlier quarters—to a consumer-level recall in April 2008 by the Actavis Group, a large generic drug manufacturer based in Iceland. The company reported "the possibility" that it had distributed double-strength tablets and recalled the entire unexpired production of its Little Falls, NJ, plant, dating back to March 2006, a total of 800 million tablets. Later the company recalled 62 products manufactured at its Little Falls plant, and the company's three New Jersey plants remain closed.

When we first learned of the scale of reported injury and death in November, we immediately notified the FDA and through the ISMP newsletter and consumer web site warned consumers and health professionals to check their supplies to ensure they did not have recalled tablets. [1] [2] The ISMP consumer website (www.consumermedsafety.org) has partnered with iGuard.org to provide help in identifying the recalled tablets. While most cases of patient injury and death could be linked to patients who reported having taken the recalled tablets, the evidence was less clear whether they had received tablets that were overstrength or had other specific defects. This is because a small overdose of digoxin can be toxic to vulnerable heart patients even without an overstrength tablet, and the recall notices could have simply alerted thousands of patients to the well-established dangers of this drug.

The existing evidence does not permit us to either rule out, or state definitively, whether defective digoxin tablets led to hundreds of patient deaths. We analyze the data and examine the unanswered questions in a separate section of this report.

Montelukast (SINGULAIR)

A second signal showed a sudden surge of reports of aggressive and suicidal behavior in children and adults taking the asthma drug montelukast (Singulair). In this period, montelukast accounted for more possible cases of depression/suicidal behavior, hostility/aggression and psychosis than any other prescription drug.

We believe this surge in reports was triggered by an FDA public notice in March 2008 that it was studying a possible link between montelukast and these psychiatric adverse effects. By alerting parents and patients to the possibility that these adverse effects could occur, the notice spurred large numbers of reports to the FDA and the drug's manufacturer, Merck & Co. Prior to the FDA notice similar reports had been received but they were small in number. These reports provide a clear signal that further investigation is required to establish or rule out a direct causal relationship.

Varenicline (CHANTIX, CHAMPIX)

In the second quarter varenicline (Chantix, Champix), a drug to aid smoking cessation, continued to account for large numbers of reported serious adverse drug events. With 910 newly reported cases of serious injury or death, varenicline ranked second only to digoxin among all prescription drugs. In addition to psychiatric side effects about which the FDA has required warnings, evidence continued to accumulate linking varenicline to potentially life-threatening allergic reactions and to increased risk of accidents.

The Adverse Event Reporting System

Reports from health professionals increased in the first two quarters of 2008 by 42% compared to the mean of the four quarters of 2007. Reports from consumers increased slightly more, by 46% in 2008 compared to the average for 2007. We estimate that approximately 2% of this increase occurred because of the technical adjustment for certain reports described below.

The FDA clarified, at our request, an ambiguity in its guidance for analyzing adverse events that were directly reported to the agency, rather than through manufacturers. It previously had been impossible to separate reported events that were "other than serious" from cases that were "other medically serious." The clarification led to our capturing an additional 2109 serious events in the second quarter that would have otherwise been excluded as "other than serious."

Conclusions

The results of the latest QuarterWatch expose two shortcomings in the system for protecting patient safety and minimizing the risks of valuable prescription drugs.

The size and scope of the digoxin recall, together with six other major recalls in 2008, show that large quantities of important generic drugs are not being manufactured to adequate quality specifications. We recommend creating a task force to conduct an independent review of the FDA's systems for inspecting companies, notifying consumers about recalls, and assessing possible harm to patients.

The discovery of hundreds of possible cases of serious psychiatric side effects of montelukast 10 years after its original approval—combined with previous reporting on varenicline (Chantix) —suggest that current clinical testing standards may be inadequate to detect psychiatric side effects prior to approval.

Furthermore, in both cases, modest public notices issued by the FDA triggered an outpouring of adverse event reports, once patients and doctors started to make the connection between the symptoms and the drug. This response suggests the extent to which patient injury associated with prescription drug therapy is being routinely underreported.

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Background

QuarterWatch is a pilot program designed to improve patient safety by monitoring serious adverse drug event reports submitted to the Food and Drug Administration. The three goals of the program are: 1) to examine overall trends in reported deaths and injury associated with drug therapy, 2) to identify signals for specific drugs that might indicate a new risk to patient safety, 3) to improve the quantity and quality of reports flowing through the voluntary system.

QuarterWatch is based on adverse drug event reports best known to consumers and health professionals as "MedWatch" reports. The serious adverse drug event reports analyzed for QuarterWatch have a unique set of strengths and weaknesses that must be considered when interpreting the results of this program. In the United States, the primary tool for monitoring the safety of drugs after FDA approval is the agency's Adverse Event Reporting System (AERS), which receives and stores adverse drug event reports it receives directly or from drug manufacturers. Approximately 70% of the reports of serious injury originate with drug manufacturers. The FDA publishes computer extracts of all reports for research use after removing personal identifying information. QuarterWatch evaluates these reports on a quarterly basis.

However, the system relies on voluntary reports from consumers and health professionals who provide information to the FDA or to drug manufacturers. What fraction of adverse events are reported is unknown, and may vary widely over time, between drugs, and among different kinds of adverse events. This means the totals for deaths and injury in this report are a small proportion of those actually occurring. In addition, the submission of an adverse event report does not in itself prove that the suspect drug caused the adverse event--it only shows that an observer suspected a link. Other factors, however, may strengthen the evidence of a causal link, and adverse event reports form the basis for many official actions by the FDA and drug manufacturers including major warnings and drug withdrawal.

One strength of the system is its sensitivity. With millions of patients and hundreds of thousands of health professionals as observers, and no restrictive rules for reporting, the system is capable of detecting adverse drug effects that may have been overlooked or underestimated in clinical testing prior to approval. Doctors, pharmacists and patients may identify an adverse effect overlooked by experts who may have preconceptions about what the drug does, or be bound by restrictive testing protocols.

We have examined the system in greater depth in previous reports.[3] Typically the data produce what we describe as signals of a problem that often requires further investigation.

Methodology

We have previously described our methodology for analyzing the quarterly FDA releases of computer excerpts of adverse event reports. [3] We limit our analysis to adverse drug events that are serious, occurred in the United States, and were not part of a clinical study or subject to other mandatory reporting rules. We standardize drug names and classify adverse event types using Standardized MedDRA Queries (SMQs), a tool developed by the pharmaceutical industry to identify possible cases for further evaluation.[4]

In this report, however, we have revised our methodology in a manner that affects the results overall and may have a significant effect on specific drugs. Previously we identified an ambiguity in those reports which were submitted directly to the FDA rather than through drug manufacturers. Numerous reports contained a computer code about the health outcome that could have meant either "Other than serious" (e.g. not serious) or "Other medically serious." We requested that the FDA clarify this issue.
The FDA responded to our request by tracing the ambiguity to a change in the MedWatch reporting form in 2005. After January 2006 the code unambiguously described serious adverse events. We had been excluding all such events because they might not be serious. An example of such an "other medically serious" case might be an episode of drug-related convulsions that did not result in hospitalization or require other medical intervention once the drug was discontinued. We appreciate the FDA's response to our request for clarification and have recommended that they include this information in the official documentation for use of the AERS data. The results of the change are described below where relevant.

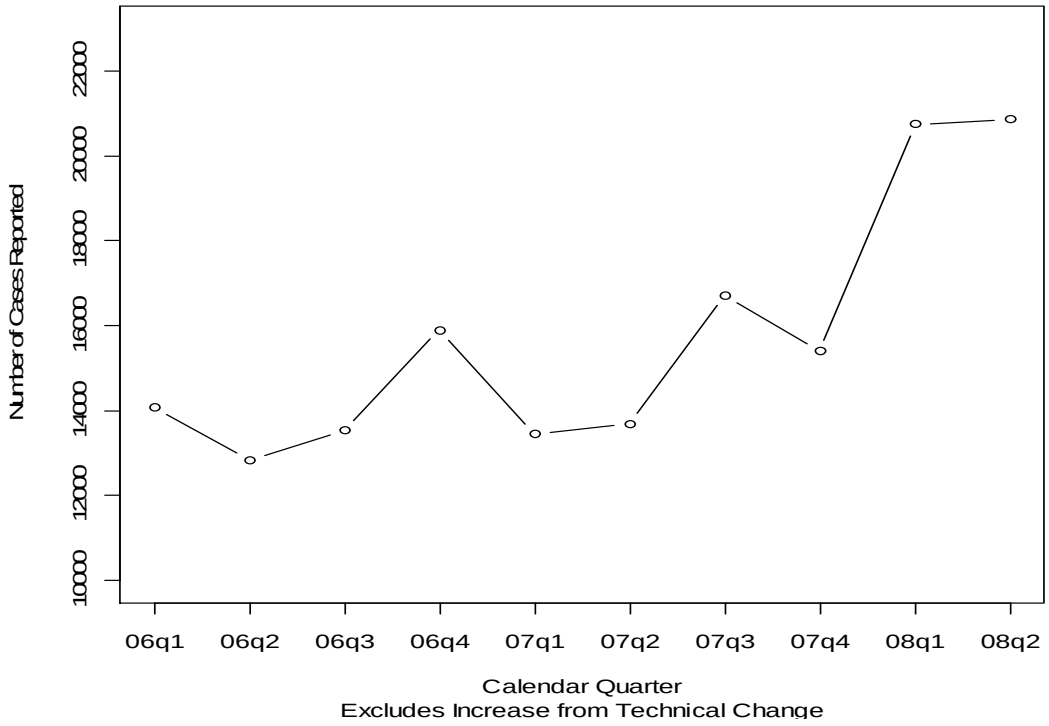
The data for this report were analyzed and the figures drawn using the open-source statistical software of the R Project for Statistical Computing.[5]

Results

In the second quarter of 2008 we identified 22,980 new cases of serious injury, disability or death associated with prescription drug therapy in the United States, an increase of 10.7% from the previous quarter. However, practically all of the increase 2109/2235 cases (94%) was due to our capturing additional serious events that had been previously classified as non-serious and therefore excluded. Therefore, we conclude that the number of reported serious events were largely unchanged from the previous quarter. The trends (before the technical change) are shown as Figure 1.

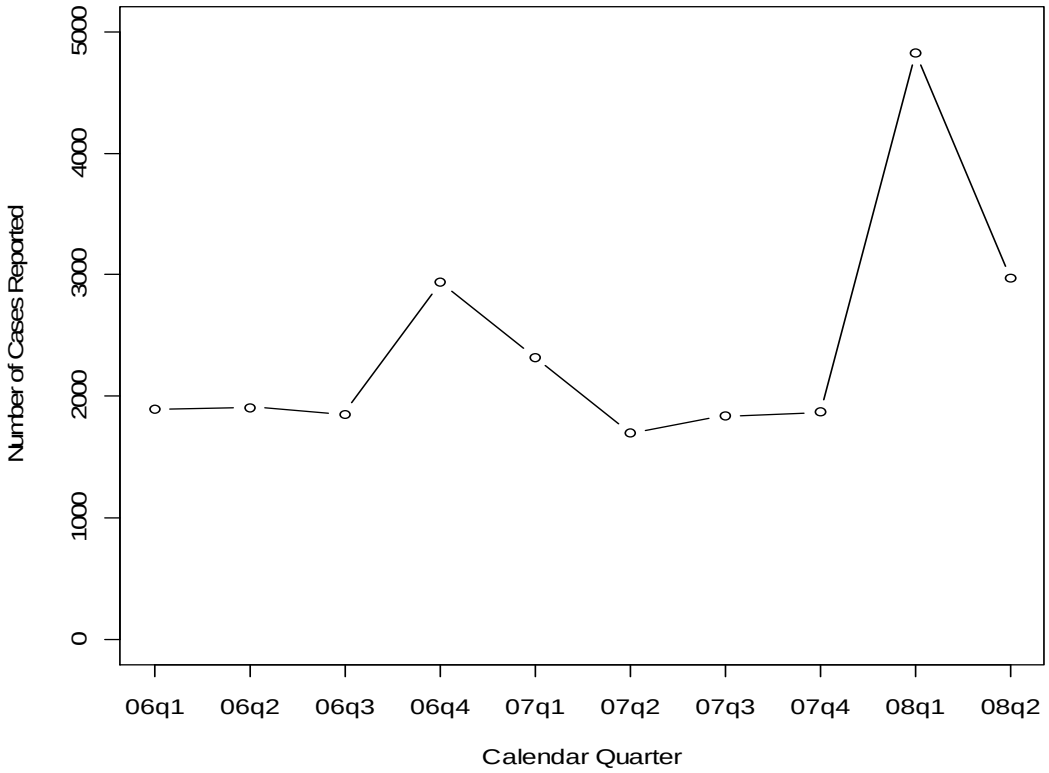
The most notable trend, however, is that for the first half of 2008, reported adverse events were 42% higher than the quarterly average for the four quarters of 2007. After adjusting for the effects of the technical change, reported adverse events in 2008 were still 40% higher than the average for 2007. The increase came about equally in reports originating from health professionals (up 42%) and from consumers (up 46%).

Figure 1. Serious Injuries Reported to FDA by Calendar Quarter



The trends for reported patient deaths show a different pattern. In the second quarter of 2008, patient deaths declined by 38%, from a record high of 4824 deaths to 2968 deaths. As reported previously, [3] we found some patient death reports in the first quarter may have been erroneous because of interpretation of a single published report of hundreds of cases that came from the nation's poison control centers. Nevertheless, quarterly patient deaths for the first half of 2008 were more than double the average seen in the preceding year, a bigger difference than for all types of serious reports together. The changes in reported patient deaths are shown in Figure 2.

Figure 2. Deaths Reported to FDA by Calendar Quarter



Results for Specific Drugs

The prescription drugs identified most frequently as the principal suspect drug in cases of death, disability or serious injury are shown in Table 1. Most notable is digoxin, which not only ranked first among all prescription drugs, but also accounted for more than twice as many serious adverse events as the second-ranked drug, varenicline (Chantix), an aid to stopping smoking and the subject of previous QuarterWatch reports. In an approximate tie for third place are three drugs, interferon beta, a treatment for multiple sclerosis, montelukast, a drug for asthma that is discussed in a separate section; and heparin, a drug to prevent or help dissolve unwanted blood clots. Heparin was involved in a large recall in the first quarter after contamination of this drug was traced to a supplier in China.[6] It should be noted that the results in Table 1 are by no means typical of most drugs. In the second quarter the FDA received serious adverse event reports for 839 different prescription drugs. Half the drugs accounted for six or fewer reports in the calendar quarter.

Table 1. Drugs Associated with Serious Injury in 2008 Q2*

Drug Name	Cases	Rank
DIGOXIN	1882	1
VARENICLINE	910	2
INTERFERON BETA	689	3
MONTELUKAST	644	4
HEPARIN	604	5
FENTANYL	578	6
INFLIXIMAB	503	7
ETANERCEPT	414	8
ESTROGENS	352	9
INSULIN	333	10

*Count includes serious, fatal and disabling injuries

Patient Deaths

The drugs most frequently identified as a principal suspect in a fatal adverse drug events are listed in Table 2. The most striking feature in this table is the 650 patient deaths attributed to the first ranked digoxin. This is a five-fold increase above the second ranked drug, ibandronate. Further, no drug has been suspect in more than 300 cases in any calendar quarter since 2006. We investigated this striking signal and ultimately linked a majority of the digoxin cases to a very large drug recall, but with important unanswered questions about the causes of death. We report our findings on digoxin and other drug recall issues in a separate section.

Table 2. Drugs associated with deaths in 2008 Q2

Drug Name	Cases	Rank
DIGOXIN	650	1
IBANDRONATE	128	2
CLONAZEPAM	120	3
HEPARIN	116	4
CAPECITABINE	110	5
METHADONE	90	6
RITONAVIR	78	7
ISOTRETINOIN	71	8
FENTANYL	58	9
INTERFERON BETA	56	10

Specific Adverse Reactions

We monitor the types of adverse reactions reported, and the drugs implicated, using Standardized MedDRA Queries (SMQs). As the table shows, in some cases the same drugs listed prominently in the table of overall events also lead certain adverse reaction categories—in this case cardiac arrhythmia and digoxin and depression/self injury and montelukast. But SMQs also permit seeing potential signals from much smaller numbers of cases in some instances.

The serious cutaneous category describes extreme, painful and potentially fatal allergic reactions that while rare are of clinical importance. We note that capecitabine, a synthetic blood thinner, and lamotrigine, a treatment for epilepsy and bipolar disorder, have prominent, black box warnings about possible severe allergic reactions. Varenicline, however, does not have such a warning.

Table 3. Selected Reactions in 2008 Q2*

SMQ/Drug	
Cardiac Arrhythmia	
DIGOXIN	546
HEPARIN	103
VARENICLINE	77
Depression/Self Injury	
MONTELUKAST	485
VARENICLINE	373
FENTANYL	86
Severe Cutaneous	
CAPECITABINE	13
LAMOTRIGINE	12
VARENICLINE	11

*Standardized MedDRA Queries (broad scope)

Varenicline Update

Background

Varenicline (CHANTIX) is a drug treatment approved to help people stop smoking. It is an alternative to numerous nicotine replacement products and Zyban (bupropion), an antidepressant drug. Since approval it has been subject to an FDA Early Communication, two FDA Public Health Alerts, a required patient Medication Guide and an FDA requirement for a risk management plan.[3] All of these actions focused on psychiatric side effects including suicide, aggression and other abnormal or violent behavior. In addition, ISMP issued a special report about varenicline in May 2008 noting that in the fourth quarter of 2007, it accounted for more reported serious injuries than any other drug. [7] ISMP described an array of possible other side effects, including a risk of accidents, possible risk of diabetes, allergic reactions and cardiac adverse effects. QuarterWatch updated its findings on varenicline for the first quarter of 2008 in its previous report.

Results

Reports of serious injury, disability and death declined for varenicline in the second quarter, but still accounted for more cases than any other prescription drug except digoxin. We identified 910 new cases in the second quarter, including 36 patient deaths. The results cannot be compared directly to the previous quarter with 1001 cases because the new QuarterWatch criteria captured an additional 148 cases that would have been excluded in the previous quarter.

Reports in the second quarter reinforced our previous concerns that varenicline could cause or contribute to a wide variety of types of accidents. Varenicline has a mechanism of action that can interfere with cognition and memory, affect sensory input such as vision, and impair muscle control. Evidence of all three of these effects was observed in the second quarter reports. We identified 6 additional reports of road traffic accidents associated with varenicline, bringing the total to 34 cases. However, many other reports indicated adverse effects with a high potential to cause accidents, including 37 cases of abrupt loss of consciousness, 18 cases of convulsions, 11 cases of impaired vision and 13 cases of muscle spasm. It is possible that a single case could involve more than one of the conditions described above.

Evidence continued to accumulate that varenicline may cause painful and life-threatening allergic reactions involving the skin. In the second quarter we identified 11 new cases of possible severe cutaneous adverse events, bringing the total to 60 possible cases. These event reports contained standardized medical terms that included Stevens-Johnson syndrome and skin exfoliation, a life threatening loss of large areas of skin. Less severe but more numerous reported cases indicated outbreaks of hives, and swelling of the eyes, lip, face, tongue and throat.

Psychiatric side effects continued to account for a majority of adverse events reported for varenicline. Although an event frequently fell into several categories, we

identified 231 possible cases of hostility or aggression, 186 cases of suicidality and 153 cases of possible psychosis. The total included 12 new cases of completed suicide and 26 suicide attempts. However, the most common reported evidence of suicidality was suicidal thought or ideation, indicated in 133 cases. As above, these categories were not at all mutually exclusive and one case frequently fell into more than one SMQ grouping.

Discussion

We continue to have concerns about the safety profile of varenicline, as first described in our special report in May 2008. The Federal Aviation Administration, as well as the Departments of Transportation and Defense, acted promptly to ban varenicline in the most accident-sensitive occupations. However, nine months later, neither the FDA nor the manufacturer has updated the Medication Guide for patients, and the prescribing information for doctors has not been updated to include a prominent warning about this drug risk.

Also of concern is the mounting number of severe allergic reactions. Given that the two drugs with similar numbers of reported severe cutaneous adverse events in the second quarter already have black box warnings, a similar warning for varenicline should be considered.

We continue to recommend that physicians consider alternative treatments to varenicline. If prescribed, we recommend that doctors tell all patients about the potential accident risks and insure patients have read and understand the following language in the FDA-approved Medication Guide:

> "If you, your family or a caregiver notice agitation, depressed mood or changes in behavior that are not typical for you, or if you develop suicidal thoughts or actions, stop taking CHANTIX and call your doctor right away."[8]

Digoxin (DIGITEK brand)

Background

In April 2008 the Actavis Group announced the voluntary Class I, consumer level recall of 800 million digoxin tablets, the entire unexpired production of its Little Falls, NJ plant over a 26-month period, and about 60% of the entire U.S. supply of an important generic heart drug. [9] [10] [11] A Class I recall, according to FDA regulation, occurs in cases where there is "a reasonable probability...a violative product will cause serious adverse health consequences or death." [12] Digoxin is one of the oldest heart drugs, discovered more than a century ago, and used in patients whose failing hearts are causing serious medical consequences.[13] Digoxin is also a narrow therapeutic index drug, meaning in this case that a small overdose can have life-threatening consequences. Digoxin overdose cases are a regular cause of hospitalization among patients with heart failure, although such cases are believed to have declined in recent years. [14]

The company stated that the reason for the recall was "due to the possibility that tablets with double the appropriate thickness (and potentially overstrength) may have been commercially released." [9] The digoxin tables were manufactured under the "Digitek" brand name, but all the tablets were sold to another generic pharmaceutical firm, Mylan Pharmaceuticals, which in turn distributed the drugs under the "Bertek" and "UDL Laboratories" trade names. In addition to possible double-thickness tablets, there was extensive evidence of manufacturing quality control problems at Actavis' plant in Little Falls, NJ. The FDA sent warning letters to the company in 2006, 2007, and 2008 citing a variety of deficiencies, including failure to investigate adverse events reported as possibly associated with defective drug products.[15] Following the digoxin recall the company recalled 62 other products manufactured at its Little Falls plant [16] and temporarily closed it and two other New Jersey manufacturing facilities. In November the Department of Justice filed suit against Actavis seeking to bar manufacturing at any of the three closed plants without the FDA's certifying that its quality control procedures met federal standards. [15] Actavis, a privately-owned generic drug manufacturer with plants in 24 countries and a headquarters in Iceland, is not manufacturing digoxin in the United States at present.

Although this is one of the largest Class I drug recalls we know of—affecting more than 1 million vulnerable heart patients—the FDA allowed the company to manage public notification of consumers, doctors, pharmacies and wholesalers. The public notice from the Center for Drug Evaluation and Research was a reproduction of a brief company statement. [9] The company stated that it had no evidence that any defective tablets had in fact entered commercial distribution, and that it had recalled nearly 1 billion tablets and closed its plants "out of an abundance of caution." [17] The QuarterWatch focus on the digoxin recall was triggered when a strong signal of a potential safety problem was seen.

Results

To study the digoxin signal we selected all digoxin adverse event reports received by the FDA since January 2006, including events that were not serious but might reveal a connection to defective tablets.

We classified all cases as definitely, possibly or not associated with the recall. To qualify as definite,a case had to be received by the FDA after the recall was announced on April 24, 2008, and contain one or more of the following items of positive identification: 1) originate from the company; 2) specifically identify the recalled tablets with the "Digitek" brand name, or 3) name of one of the two distributors, Bertek or UDL Laboratories. We classified as not associated with the recall the following: 1) reports identifying another brand name drug, 2) submitted by a different manufacturer, 3) reports indicating a route of administration other than oral, 4) containing a term describing a medication error, or 5) indicating an event date before the recall period began on March 1, 2006. If the case was received in the recall period, but contained no other information to either qualify it as definite or exclude it, the case was classified as possible. The results are shown in Table 4.

Table 4. Digoxin Adverse Event Reports 2006 to 2008 Q 2 By Recall Association

Outcome Group	Definite N (pct)		Possible N (pct)		Not N (pct)		Total N (pct)	
Total	1690		289		424		2403	
Death	612	(36.2)	18	(6.2)	72	(17.0)	702	(29.2)
Disability	21	(1.2)	3	(1.0)	8	(1.9)	32	(1.3)
Serious	868	(51.4)	91	(31.5)	271	(63.9)	1230	(51.2)
Other	189	(11.2)	177	(61.2)	73	(17.2)	439	(18.3)
Report Type								
Direct to FDA	474	(28.0)	289	(100.0)	245	(57.8)	1008	(41.9)
Mfr-Expedited	1216	(72.0)	0	(0.0)	149	(35.1)	1365	(56.8)
Mfr-Periodic	0	(0.0)	0	(0.0)	30	(7.1)	30	(1.2)
Report Source								
Consumer	1322	(78.2)	51	(17.6)	143	(33.7)	1516	(63.1)
Health Professional	166	(9.8)	189	(65.4)	212	(50.0)	567	(23.6)
Lawyer	7	(0.4)	1	(0.3)	0	(0.0)	8	(0.3)
Other	2	(0.1)	0	(0.0)	1	(0.2)	3	(0.1)
None Stated	193	(11.4)	48	(16.6)	68	(16.0)	309	(12.9)

These data show that among 2403 adverse event reports received since January 2006, 1979 (82%) were definitively or possibly associated with the digoxin recall. This included 630 (89%) of the patient deaths. Compared to other drugs, these cases were more likely to involve a patient death and more likely to have been received directly by the FDA rather than through the manufacturer, and to have originated from consumers, rather than health professionals.

We also examined the potentially stronger causal link indicated by dechallenge and rechallenge cases. In a dechallenge case the adverse event observed stops when the suspect drug is stopped. In a rechallenge case an adverse event first stops when the drug is withdrawn, then resumes when it is started again.

We identified 233 dechallenge cases among those definitely associated with the recall and 14 rechallenge cases. Among those cases possibly associated with the recall we identified 42 dechallenge cases and 7 additional rechallenge cases.

Among cases associated with the recall, the patient characteristics were consistent with a population diagnosed with heart failure. The average age was 71.7 years, with one-quarter of all patients 82 years old or more. The population was divided evenly by gender, with 956 cases (49%) female and 993 cases (51%) male, and 30 cases without gender indicated.

Discussion

Because of limitations in the U.S. system for post-market surveillance, the characteristics of the drug, and the nature of the system for recalling defective drugs, it is not possible to estimate how many patients might have died or become seriously injured by defective digoxin tablets.

The available facts show that the Actavis plant had widespread manufacturing quality control problems observed over a period of several years, and has been shut down. We identified 1979 case reports as definitely or possibly associated with the recalled tablets. The strength of the signal—the high number of reported patient deaths—also indicates a problem, as do the numerous dechallenge and rechallenge cases.

Nevertheless, the uncertainties are large and important. Neither the company nor the FDA will estimate how many tablets actually reached consumers; nor will either party reveal how many tablets have been recovered through the Class I recall. Neither the FDA nor the company has tested the recalled tablets to determine how many might have been defective. Given the extensive manufacturing problems at the plant, there is no reason to suppose that the only manufacturing defect was double-thickness tablets. Neither the FDA nor the company had any information about how the recall worked at the consumer level, which was left to pharmacies and other sources of consumer-level prescriptions.

Injuries resulting from the reported defect—potentially overstrength tablets—would also be difficult to distinguish from digoxin overdose toxicity, an existing, well-documented risk of the drug. Without extensive testing of distributed and recalled tablets, it is difficult to separate cases caused by defective tablets from other causes, including declining kidney function, decreasing cardiac output and failure to monitor blood levels of the medication.

What is clear, however, is that millions of patients were exposed in 2008 to drugs linked to significant failures in generic drug manufacture quality control. In January 2008, millions of vials of heparin were recalled because of possible contamination from a supplier in China. [6] In March and April 2008, millions of defective, leaking fentanyl patches were recalled from multiple manufacturers, including the ALZA Corp (3 million cartons) [18] and Actavis (2.5 million patches).[19] In April, the Actavis Group recalled 800

million digoxin tablets. In June Actavis recalled 62 other products. In September the FDA announced it was banning the import of 32 prescription drug products from Ranbaxy, a manufacturer in India. [20] In November and December, five products with high overdose risks (including amphetamines and morphine) were recalled by KV Pharmaceutical and its Ethex subsidiary because of the potential for oversized tablets. [21] On December 23, KV Pharmaceutical suspended shipments of all 14 prescription drug products it manufactured in tablet form. [22] On December 22 the FDA sought the recall of 25 different over-the-counter weight loss pills (dietary supplements) citing the risk of high blood pressure, seizures, palpitations, heart attack and stroke. [23]

That we cannot reliably estimate how many patient injuries and deaths occurred from defective pharmaceuticals speaks clearly to the need to improve the system. The true number of patient deaths could range from relatively small numbers to thousands.

Montelukast (SINGULAIR)

Background

Montelukast (SINGULAIR) was first approved in 1998 and is currently indicated for the treatment of asthma and seasonal allergies in adults and children over 12 months of age.[24] The drug blocks the action of chemical messengers called leukotrienes, which play a role in the inflammatory response of the body. The company states that animal studies indicated the drug has minimal distribution across the blood-brain barrier. The product label contains no mention of psychiatric side effects in the sections providing information for patients, or recommending precautions or providing warnings. However, under the section "Post-Marketing Experience" the company lists among adverse reactions reported: "Psychiatric Disorders: agitation including aggressive behavior, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), tremor."

On March 27, 2008, the FDA publicly announced it was conducting a safety review of montelukast regarding "a possible association between the use of Singulair and behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide." [25] The announcement was a relatively new kind of preliminary statement for the public called an "Early Communication." This low-key statement contained cautionary language indicating the agency had not reached any conclusions, and would study the issue for the next nine months. Neither the FDA nor the company provided any information about the number of adverse event reports that had been received about psychiatric side effects.

Montelukast is a widely used prescription drug, the 8th most frequently prescribed drug in 2007, accounting for 31 million prescriptions.[26]

Results

In the second quarter of 2008, we identified 644 serious, disabling or fatal injury cases identifying montelukast as the principal suspect drug. The total included 26 reported patient deaths with 8 occurring in children under 18 years of age.

Measured by SMQs, montelukast accounted for more possible cases of depression/suicidal behavior, hostility/aggression and psychosis than any other drug taken for any purpose in the second quarter. Because of how the categories are structured, a single event frequently fell into more than one category of psychiatric event. For serious adverse drug events of all types, montelukast ranked fourth in the second quarter, its first appearance among the 10 highest ranked drugs accounting for reports of serious or fatal injury. (Table 1) To investigate this striking signal we analyzed all serious adverse event reports for montelukast received by the FDA since January 1, 2006.

We identified a total of 918 case reports since 2006, including the 644 (71%) received in the second quarter. These data emphasized the major surge in reports following the FDA's March 27, 2008 Early Communication. In all, 712 (78%) of all

cases reports were received in the 13 weeks after the FDA notice, compared to 206 (22%) reports in the 116 weeks prior to the notice.

We also separated the cases into two categories, possible psychiatric side effects and all other side effects. A case was classified as a psychiatric side effect if it fell into one or more of the following Standardized MedDRA Queries (SMQs): Depression/Self Injury, Hostility/Aggression or Psychosis. It should be noted that SMQs are designed to identify possible cases for further analysis and are not definitive event classifications.

The results further indicate an effect of the FDA Early Communication. The agency had received 24 cases (4%) of possible psychiatric side effects before the warning, and 602 cases (96%) after the warning. The case for a possible causal relationship was strengthened by the 204 cases in which the reporter said the psychiatric adverse effect went away once drug treatment was halted. In another 40 cases, the psychiatric side effect reappeared once the drug was started again.

In addition, the psychiatric side effects were reported more frequently than other types of adverse events in children under 18 years age, compared to adults. In all, children accounted for 59% of all adverse event reports but 67% of all potential psychiatric side effects. (Chi-square = 38.55 $P < 0.01$)

We also discussed our findings with Merck. The company said it also observed a marked increase in reports in the second quarter. Officials told us they expected to observe such an increase following the FDA's Early Communication and that the increased number of reports did not establish causality. They noted that Merck already had moved expeditiously, on the basis of a much smaller number of reports, to include information about psychiatric disorders in the product label at various times prior to the FDA's Early Communication.

Discussion

These data show that hundreds of doctors, parents and patients reported possible psychiatric side effects of montelukast, once informed of a possible connection.

A handful of cases prior to March 2008 were credible enough for the manufacturer, Merck & Co., to include them in the product information for physicians, and to trigger an independent FDA safety review, without either indicating it had confirmed a causal relationship. The mere public notice that such a review had begun, together with the addition of suicide to the product label, was enough to trigger hundreds of additional case reports.

For an event to be reported in a voluntary system, a linked series of events has to happen: 1) it has to occur; 2) it has to be observed in credible detail; 3) a connection to the drug has to be suspected, and 4) the observer must elect to report it. The case of montelukast illustrates what happens when one link in this chain—a connection to the drug—is largely missing, and what occurs when healthcare professionals and consumers are informed of a possible connection.

In the past, drug manufacturers have sought to discount spikes in adverse event case reporting when connected to publicity as “stimulated” reporting, as if the cases were somehow less valid than other reports. We believe the opposite: without patients and

doctors getting adequate information about possible drug adverse events, the injuries caused by drug therapy will be substantially underreported in any kind of monitoring system. Rather than discounting these events, such spikes are evidence of the system beginning to correct undercounting that routinely occurs.

While these reports add weight to the likelihood that these reported adverse effect may be caused by the drug, important questions are raised or left unanswered by these data.

These results provide little useful information about how rare or common these reported psychiatric side effects might be. After the FDA warning, psychiatric side effects accounted for 96% of all types of adverse events cases reported; prior to the warning the warning psychiatric side effects accounted for 4% of a small number of cases.

Furthermore, systematic analysis of these possible cases will result in many instances where the report was too vague to judge, had other information making a drug relationship unlikely, or had alternative causes. Thus the number of "confirmed" cases might be fewer than reported here.

On the other hand, montelukast has been a widely used drug for a decade. Unless one believes all of the hundreds of reported cases were invalid, it could mean these adverse effects were either undetected in clinical testing, or that early warning flags were disregarded or not appreciated. So the net underreporting of these adverse events could be large.

The belated association of psychiatric side effects with montelukast is not an isolated case. Mounting evidence suggests that the current system of drug testing and surveillance is doing a poor job in detecting psychiatric side effects. Our previous reporting on varenicline included psychiatric side effects that had not been prominent in recently completed clinical testing—the alleged gold standard for documenting the effects of drugs. [27] In December 2008 the FDA required a warning about suicidal thoughts and action for 11 different drugs for epilepsy. [28] Some of these drugs have been in clinical use for decades. Finally, in the case of newer antidepressant drugs, prominent psychiatrists first linked these drugs to suicidal thoughts and behaviors in 1990 [29] but it was not until 2004 that the first warnings began to appear.[30] We believe this problem deserves systematic study. One clear deficiency in the current system is the failure to use psychiatric symptom checklists in clinical studies for drug approval; other problems may also contribute.

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